

بسم الله الرحمن الرحيم

سُبْحَانَكَ اللَّهُمَّ



CONTRIBUTING FACTORS TO RESISTANT HYPERTENSION

Dr Samir Sally, MD

*Consultant Medicine & Nephrology,
Mansoura Urology & Nephrology
Centre*



THE LANCET

Volume 365 Number 9455 Pages 189–266 January 15–21, 2005

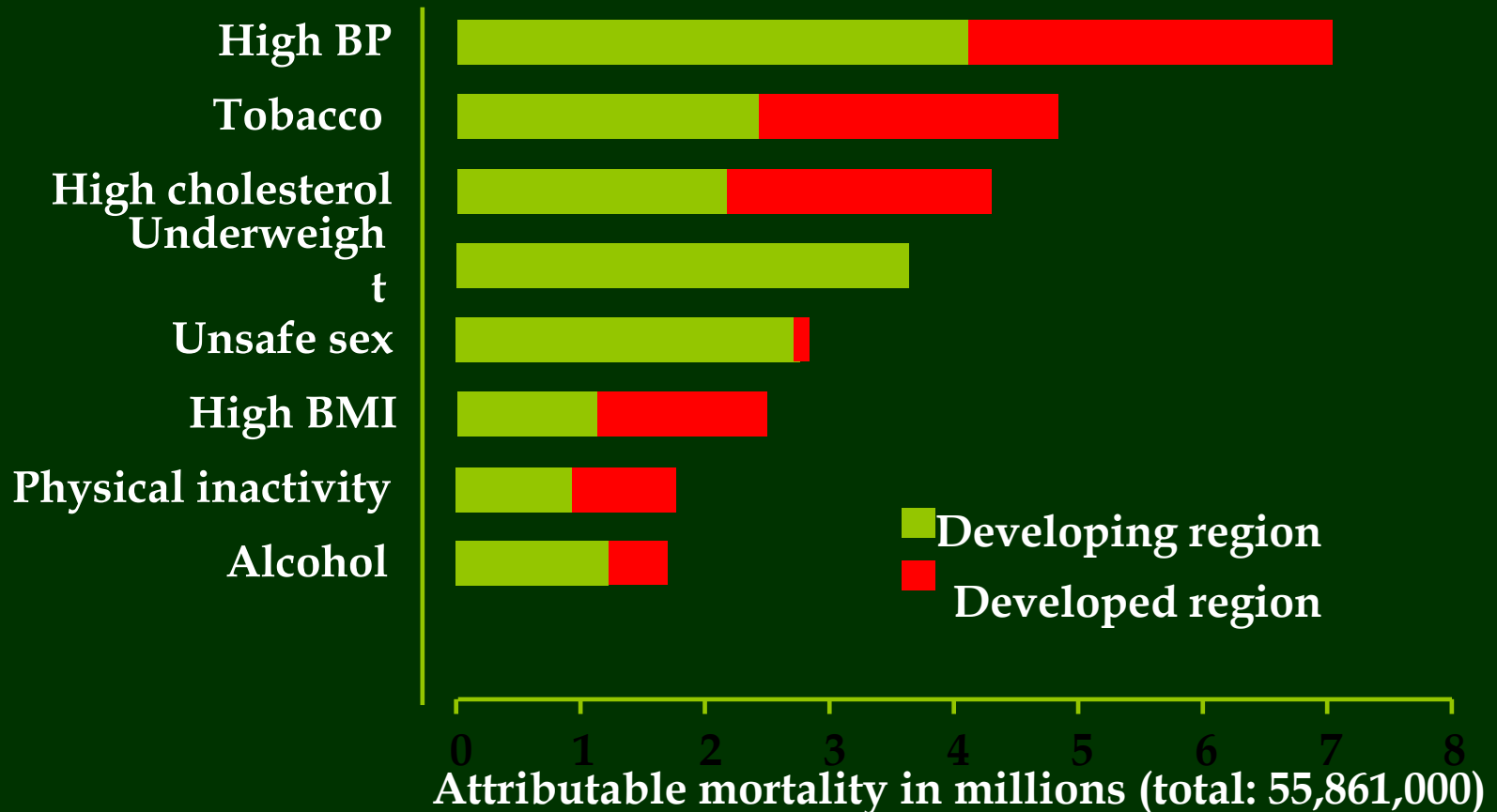
www.thelancet.com

"More than a quarter of the world's adult population—totalling nearly one billion—had hypertension in 2000, and . . . this proportion will increase to 29%—1.56 billion—by 2025."

See **Articles** page 217

Global Mortality 2000

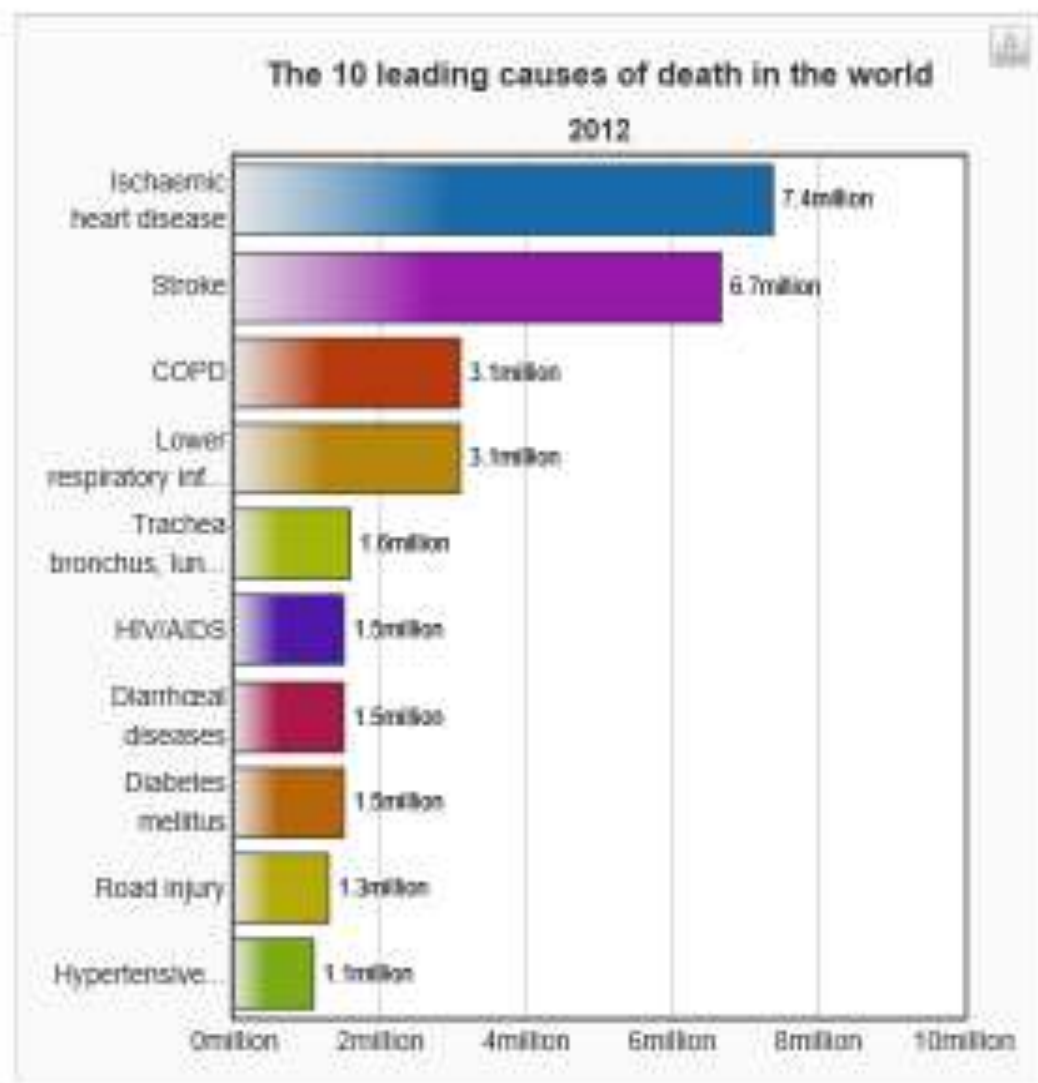
Impact of Hypertension and Other Health Risk Factors



Adapted from Ezzati et al. Lancet 2002;360:1347-60

(along with trachea and bronchus cancers) caused 1.8 million (2.8%) deaths in 2012, up from 1.2 million (2.2%) deaths in 2000. Similarly, diabetes caused 1.5 million (2.7%) deaths in 2012, up from 1.0 million (2.0%) deaths in 2000.

Related links

[Causes of death](#)

Hypertension is one of the risk factors for coronary artery disease and cerebrovascular disease ⁵



World Health Organization reports that suboptimal BP (>115 mmHg SBP) is responsible for:⁷



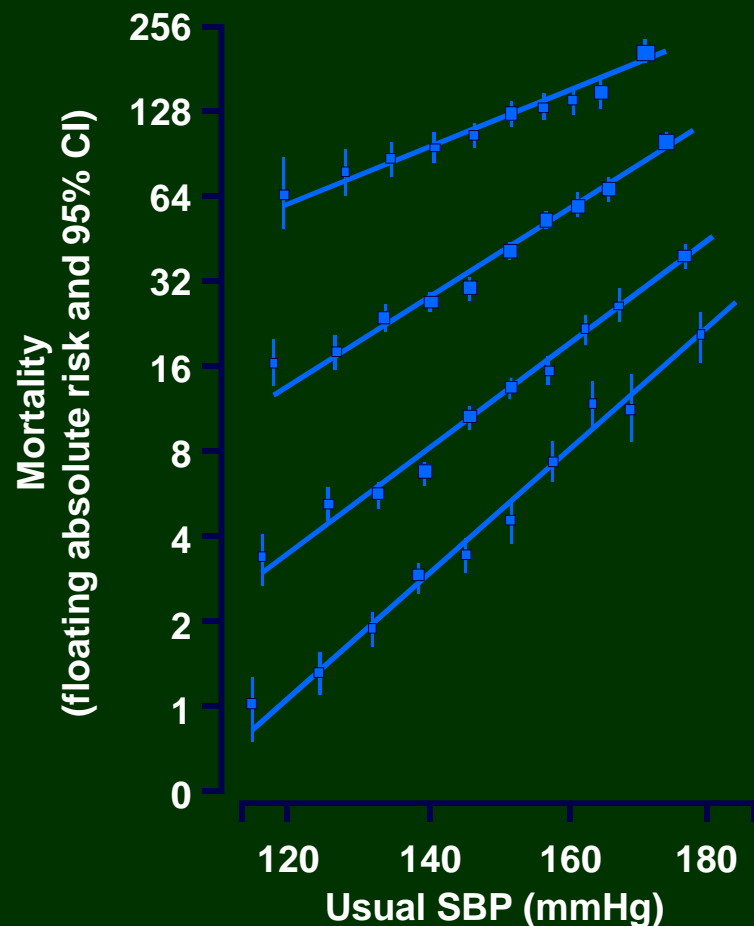
Cerebrovascular disease



Ischemic heart disease

Stroke and ischaemic heart disease (IHD) mortality versus systolic blood pressure (SBP) by age

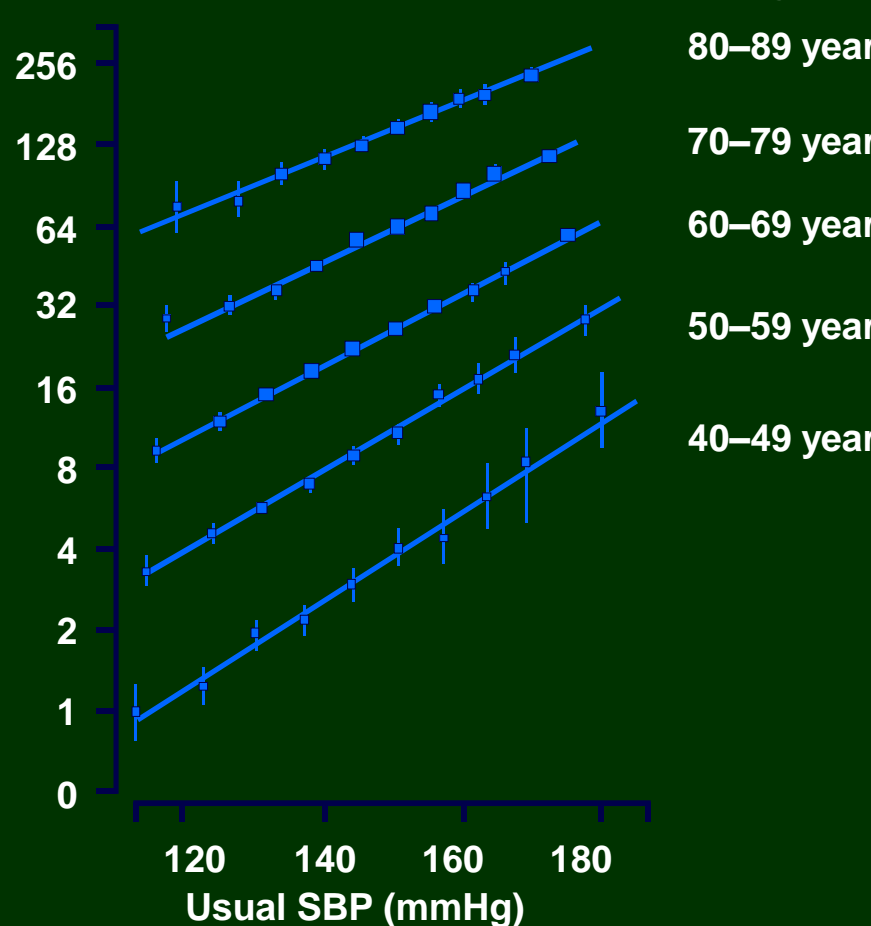
Stroke



Age at risk:

80–89 years
70–79 years
60–69 years
50–59 years

IHD



Age at risk:

80–89 years
70–79 years
60–69 years
50–59 years
40–49 years

Hypertension

- Each 2 mmHg rise in systolic blood pressure associated with increased risk of mortality:
 - 7% from heart disease
 - 10% from stroke.

Control rate maximum 40% in European countries

Achievement of treatment goals in the EURIKA study

	AUS	BEL	FRA	GER	GRE	NOR	RUS	SPA	SWE	SWI	TUR	UK	Total, n (%)
Hypertension, n	447	448	434	549	413	426	486	435	516	475	441	489	5559
Drug treated, %	92.8	96.4	97.2	97.3	97.3	90.1	85.4	92.4	96.3	95.2	94.6	95.5	94.2
Controlled (SBP <140 mmHg and DBP <90 mmHg), % ^a	35.9	43.7	45.5	36.3	47.5	34.6	35.9	41.0	33.6	37.4	32.1	42.8	38.8
Dyslipidaemia, n	368	434	336	404	450	335	305	432	313	394	229	407	4407
Drug treated, %	58.7	75.1	81.2	65.1	80.2	75.5	49.8	81.2	85.9	74.6	80.3	82.6	74.4
Controlled (TC <5 mmol/L), % ^a	32.9	54.6	39.9	33.5	39.1	45.8	27.6	32.8	48.0	45.9	30.4	70.8	43.3
Controlled (TC <5 mmol/L and LDL-c <3 mmol/L), % ^a	31.9	52.8	37.7	30.4	37.4	41.9	24.3	31.0	45.3	44.6	30.4	68.4	41.2
Type 2 diabetes, n	146	173	144	256	176	142	95	182	164	205	210	153	2046
Drug treated, %	86.3	90.7	93.7	80.9	92.0	82.4	84.2	87.9	83.5	89.8	95.2	77.8	87.2
Controlled (HbA1c <6.5%), %	39.7	48.4	41.5	40.6	43.8	41.9	26.2	33.7	23.4	41.8	26.0	27.7	36.7
Controlled (FPG <6.1 mmol/L), %	16.7	19.7	27.4	27.0	15.4	35.9	7.5	13.1	43.1	16.3	6.0	13.4	20.0
Controlled (HbA1c <6.5% and FPG <6.1 mmol/L), %	7.9	6.4	6.7	11.1	8.0	15.4	3.7	3.1	10.9	8.1	2.5	1.7	7.2
Obesity, n	315	315	217	332	311	224	342	256	235	298	240	239	3324
Treatment with lifestyle advice, %	91.7	91.7	98.2	94.6	94.5	86.2	97.7	97.6	72.3	88.6	96.2	94.1	92.2
Controlled (BMI <30 kg/m ²), %	28.0	29.2	19.6	28.8	37.1	26.7	23.3	21.1	23.3	23.8	16.1	12.7	24.7
Controlled (WC <102/88 cm), %	6.2	12.0	2.9	9.0	7.6	4.9	5.9	11.2	3.6	7.0	2.2	5.2	6.8
Controlled (BMI <30 kg/m ² and WC <102/88 cm), %	3.2	6.0	2.4	5.3	4.1	2.7	0.9	4.1	2.4	3.8	0.4	1.4	3.2

AUS, Austria; BEL, Belgium; FRA, France; GER, Germany; GRE, Greece; NOR, Norway; RUS, Russia; SPA, Spain; SWE, Sweden; SWI, Switzerland; TUR, Turkey; UK, United Kingdom; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low density lipoprotein cholesterol; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; BMI, body mass index; WC, waist circumference.

^aIf diabetes: blood pressure <130/80 mmHg, total cholesterol <4.5 mmol/L, and LDL cholesterol <2.5 mmol/L.

Banegas JR, Borghi C, et al. *Eur Heart J*. 2011.

European Heart J 2011

The overall hypertension control rate in the US hypertensive population increased from 28.7% in NHANES 2001 to 2002 to 47.2% in NHANES 2009 to 2010 ($P_{trend} < 0.01$).

<http://dx.doi.org/10.1161/CIRCULATIONAHA.112.096156> Published:
October 23, 2012

Hypertension...

A growing burden in Saudi Arabia

High prevalence of hypertension in KSA compared to other countries in Africa and Middle East



26%
of Saudi Arabia population suffer from
hypertension

1. Arnaout MS, Almahmeed W, Ibrahim M, et al. *Current Medical Research & Opinion* 2011; 27 (6): 1223–1236.

Hypertension...

A disease that requires attention



Control rate
of
hypertension
was low
25%¹

Cardiovascular
disease was
responsible for
47%
of all deaths
in Saudi Arabia¹

50% of
Saudi
diabetic patients
failed to achieve
their target BP of
130/85 mmHg¹

Prevalence, Awareness, Treatment, and Control of Hypertension among Saudi Adult Population: A National Survey

Abdalla A. Saeed, * Nasser A. Al-Hamdan, Ahmed A. Bahnassy,
Abdelshakour M. Abdalla, Mostafa A. F. Abbas, and Lamiaa Z. Abuzaid

Int J Hypertens. 2011 September 6.

Cross-sectional study. ■

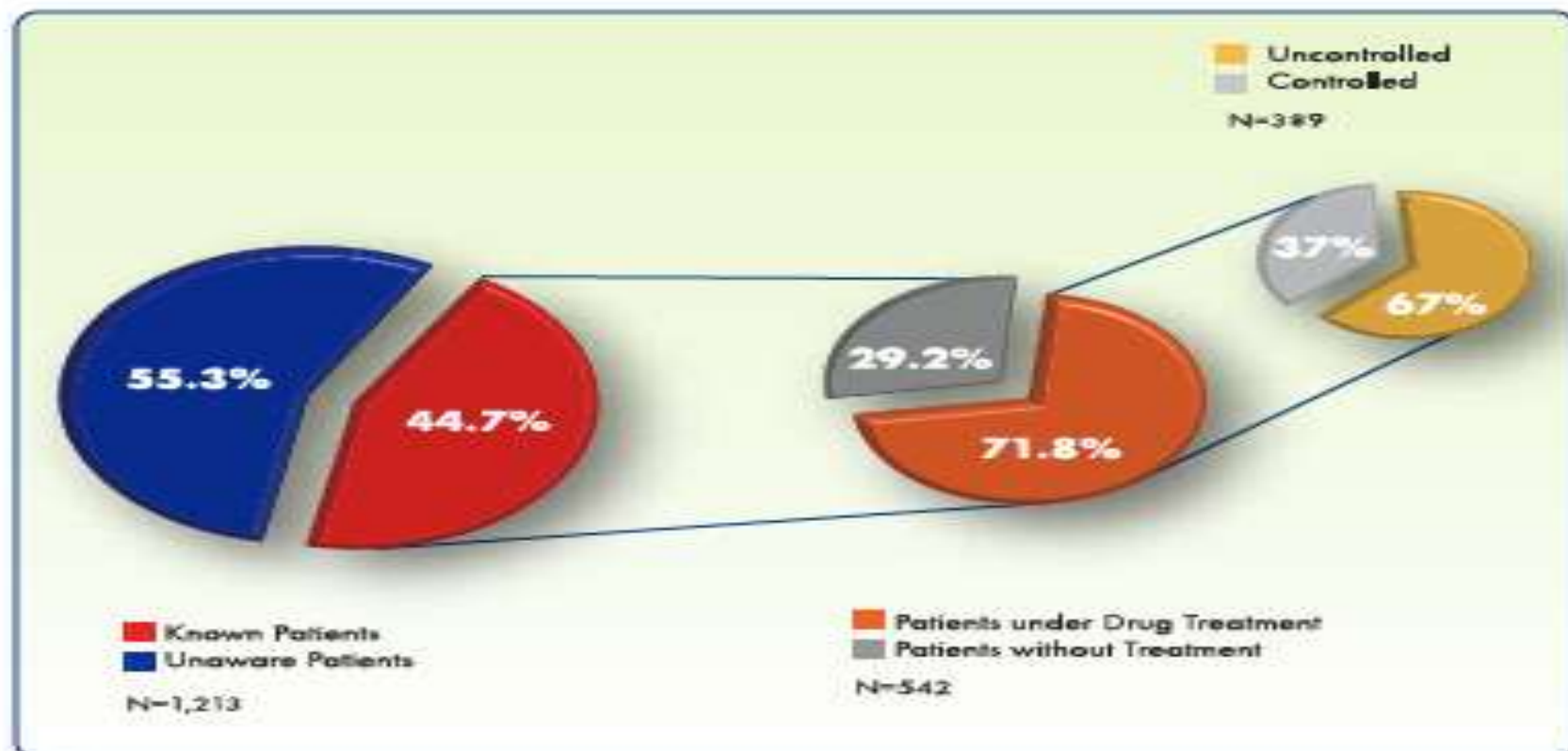
Multistage stratified sampling was used to select 4758 adult participants. ■

The overall prevalence of hypertension was ■
25.5%.

Only 44.7% of hypertensives were aware, ■
71.8% of them received pharmacotherapy, and
only 37.0% were controlled.

In 2011 National Hypertension Survey in KSA

The high prevalence of hypertension and the low levels of awareness; treatment and control all are of high importance.¹



Only **37%** of the known treated hypertensive patients were controlled (BP under 140/90 mmHg).¹

conclusion

Prevalence is high, but awareness, treatment, and control levels are low indicating a need to develop a national program for prevention, early detection, and control of hypertension

Few patients under control?



Factors Related to the Result in Poor Control Rates

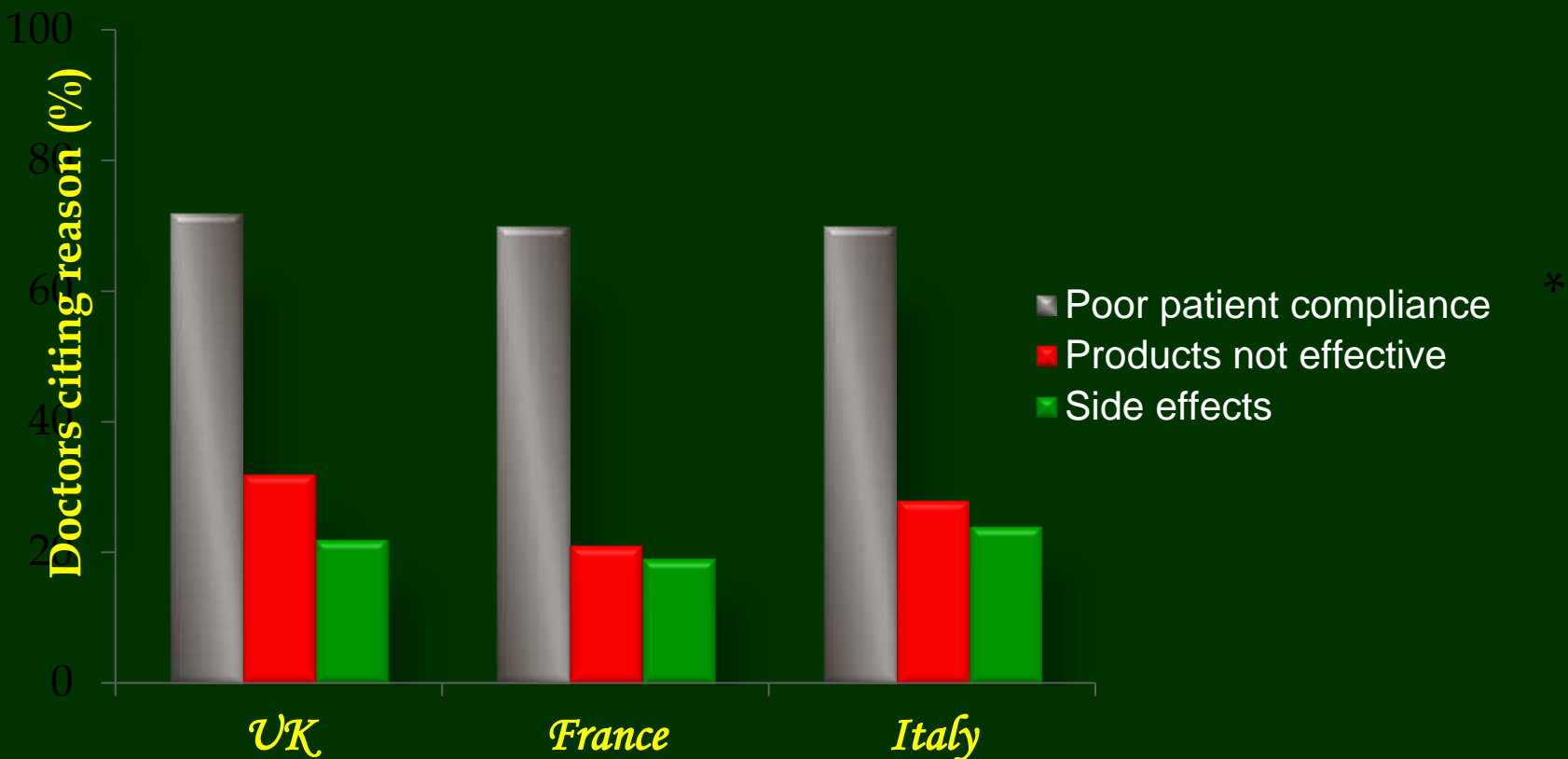
Poor Efficacy

*Adverse Side
Effects*

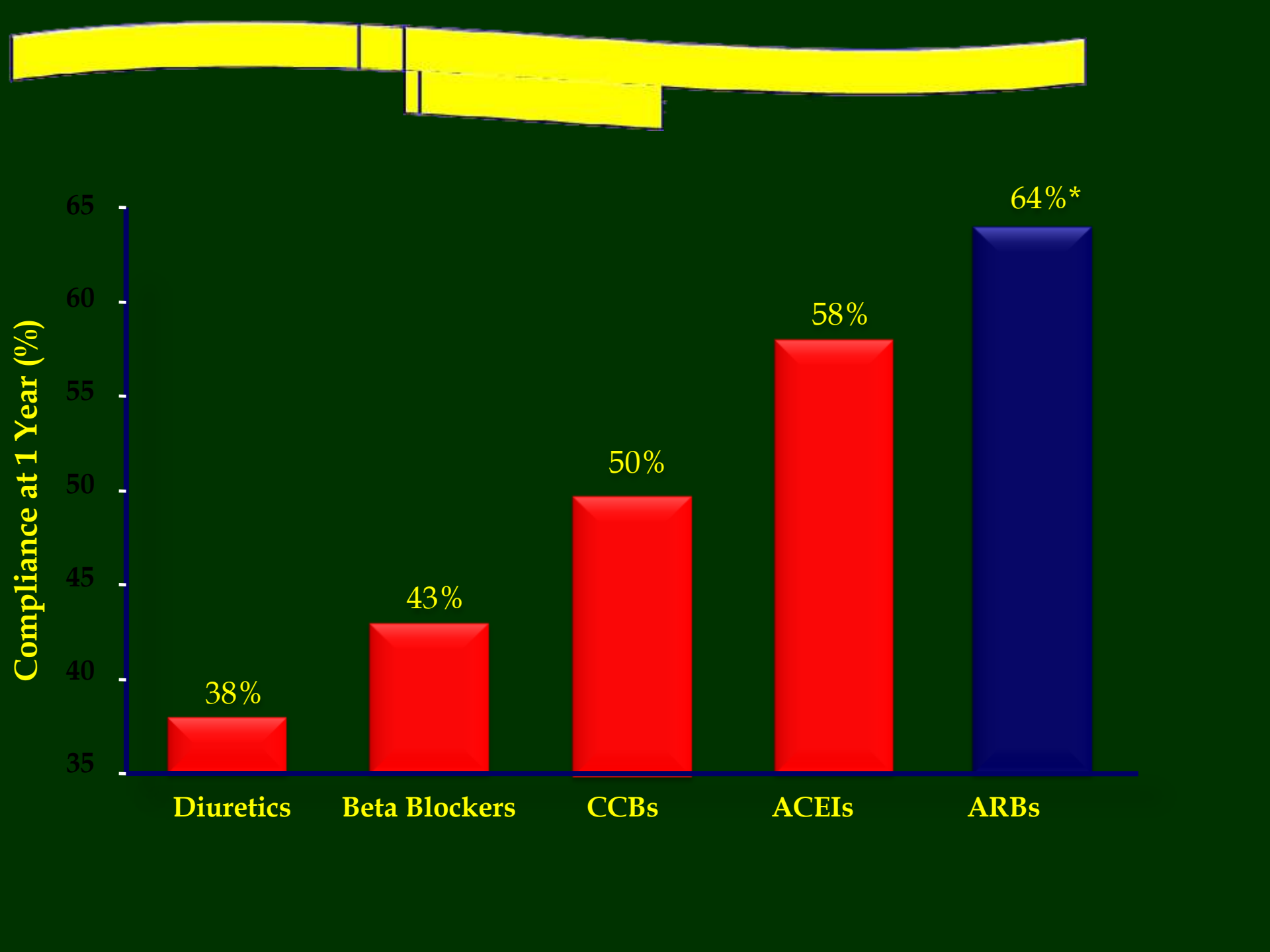
*Inconvenient
Dosing*

Poor Compliance

More Than 70% of Physicians Suspect Poor Compliance as the Reason For Antihypertensive Treatment Failure

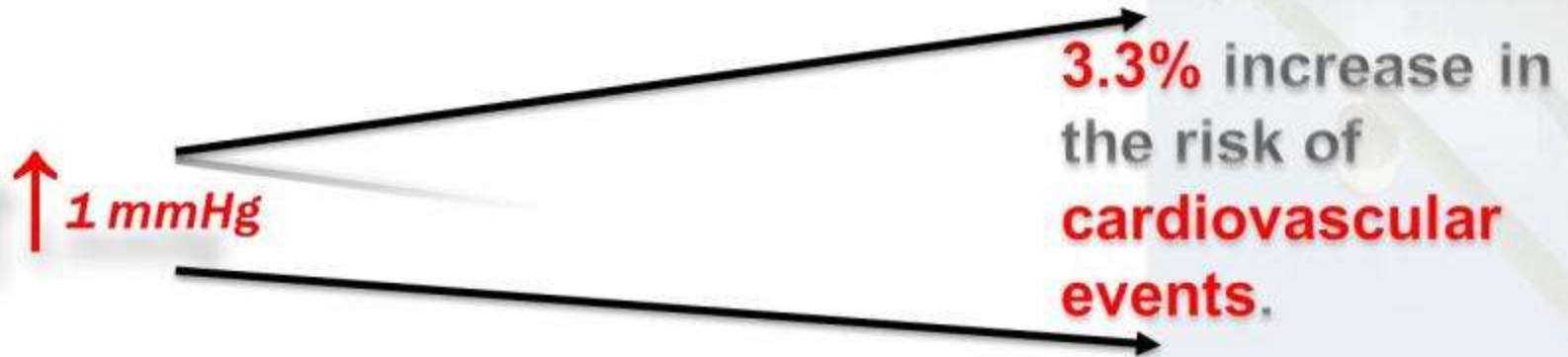


* In patient surveys, side effects are a major reason for poor compliance



Circadian Pattern of BP

Many hypertensive patients still have unmet needs



sleeping-to-waking morning pressor surge in SBP

Gosse P, Lasserre R, Minifié C, Lemetayer P, Clementy J. Blood pressure surge on rising. *J Hypertens.* 2004; 22: 1113–1118

Causes of Resistance to Therapy in Hypertension

1. Accuracy of resistance

- a) Inaccurate measurement of blood pressure
- b) White-coat hypertension
- c) Pseudohypertension

2. Non-adherence

3. Inappropriate regimen

4. Diet/Body weight

5. Iatrogenic causes

6. Secondary Hypertension

7. Sleep disorders

Rate of Non-Adherence by Disease State

Condition	Rate of non-adherence
Asthma	20%
Arthritis	55-70%
Contraception	8%
Diabetes	40-50%
Epilepsy	30-50%
Hypertension	
"Non" compliers	40%
"Partial" compliers	30%
"Full" compliers	30%

Berg JS et al, Ann Pharmacotherapy, 1993
Rudd P, Am J Managed Care, 1998

Approximately 50% of patients do not take medications as prescribed

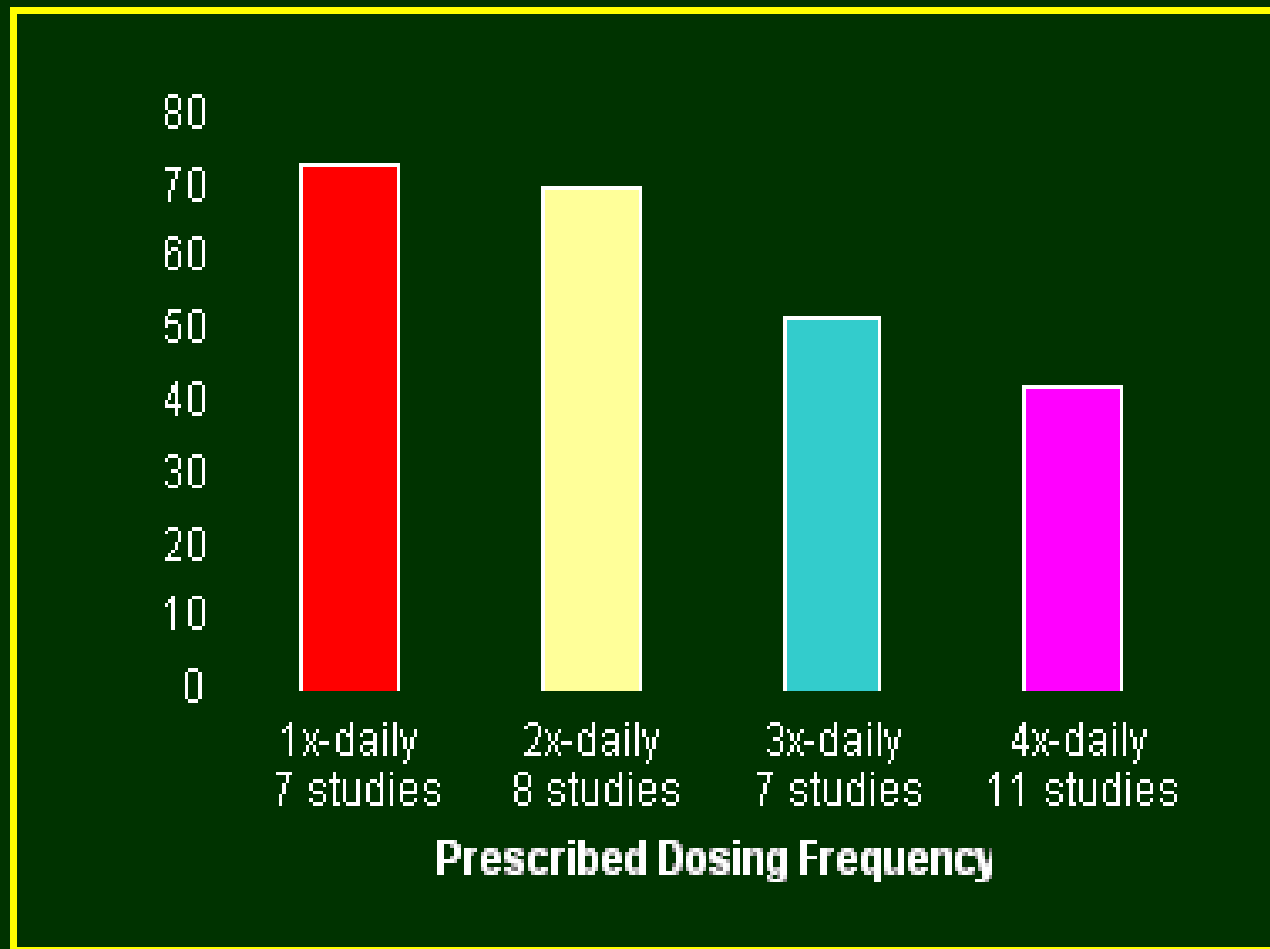
Medication adherence is not exclusively the responsibility of the patient

Medication-taking behavior is complex and involves patient, physician, and process components
Identification of nonadherence is challenging and requires specific interviewing skills

I

Journal List Mayo Clin Proc v.86(4); 2011 Apr

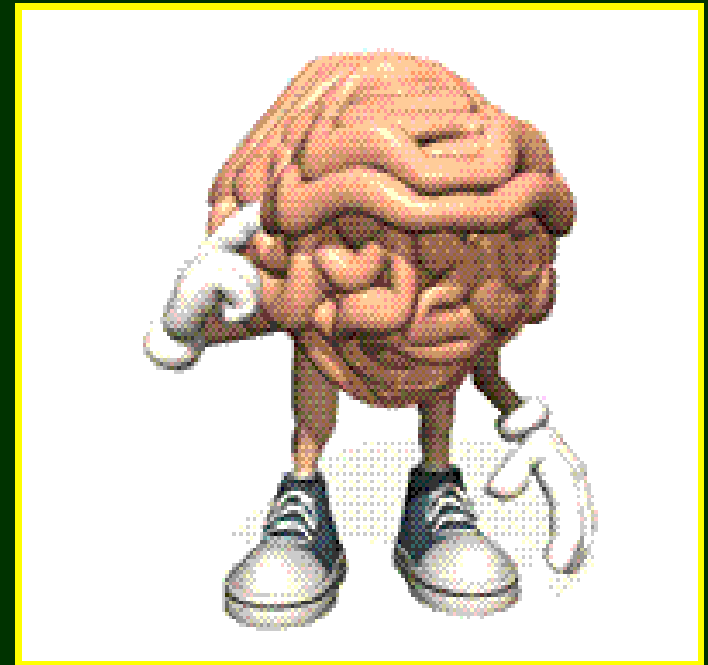
Compliance Rate by Dosing Schedule



Cause of Non-Adherence:

Confusion

- Instructions not clear and/or not given to the patient in writing
- Organic brain syndrome (e.g., memory deficit)
- Inconvenient or complex dosing schedule



Suggestions for Increasing Patient Compliance with Antihypertensive Therapy

- **Education**
- **Increase frequency of visits**
- **Self-measurements of BP**
- **Prescribe drugs least likely to result in adverse effects**
- **Prescribe a once-a-day regimen**
- **Use fixed-dose combinations**
- **Choose the least costly regimen**
- **Acknowledge progress toward goal**

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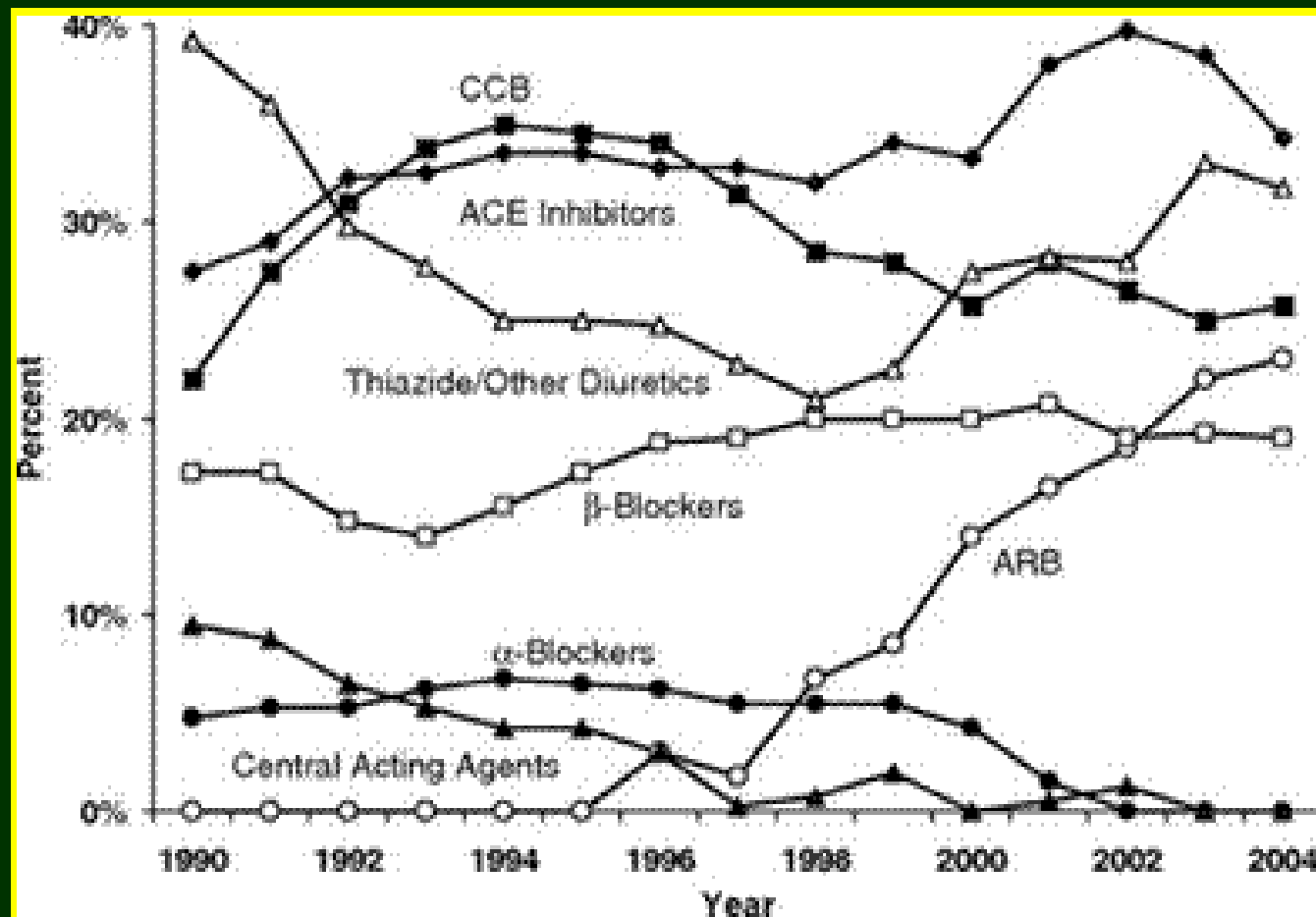
4. Diet/Body weight

5. Iatrogenic causes

6. Secondary Hypertension

7. Sleep disorders

Long-term trends of antihypertensive drug prescribing (annual data 1990-2004)



Hypertension



Clinical Hypertension 2016 22:7

Table 2

Findings from different studies conducted to evaluate prescribing pattern of antihypertensive drugs

Author name	No. subjects involved	Mono-/combination therapy prescribed	Antihypertensive drug class	Observation/Remarks
Caceres et al. [13]	100 % of the Extremadura population	Monotherapy	ARBs, ACEIs	Use of ARBs increased over ACEIs
Xu et al. [14]	59 hospitals' databases	Monotherapy	CCBs, ARBs, ACEIs, BBs, and diuretics	The top-prescribed antihypertensive drug classes were CCBs and ARBs
Liu and Wang [15]	6,536	Mono and combination	CCBs (17.7 %), CCBs + beta-blockers (7.7 %)	CCBs and BBs were the most prescribed antihypertensives

**Unless not tolerated, a diuretic
should be part of any 3-drugs
antihypertensive regimen!!!!**

Combinations of Antihypertensive Agents

Ineffective Associations

- Diuretics + Ca-antagonists ?
- β -blockers + ACE-inhibitors (or ARBs ?)
- ACE-inhibitors + AT₁-ARBs (On-TARGET Study)
- CCBs and vasodilators (hydralazine, minoxidil)

Associations with Negative Effects

- α_1 -antagonists + Clonidine

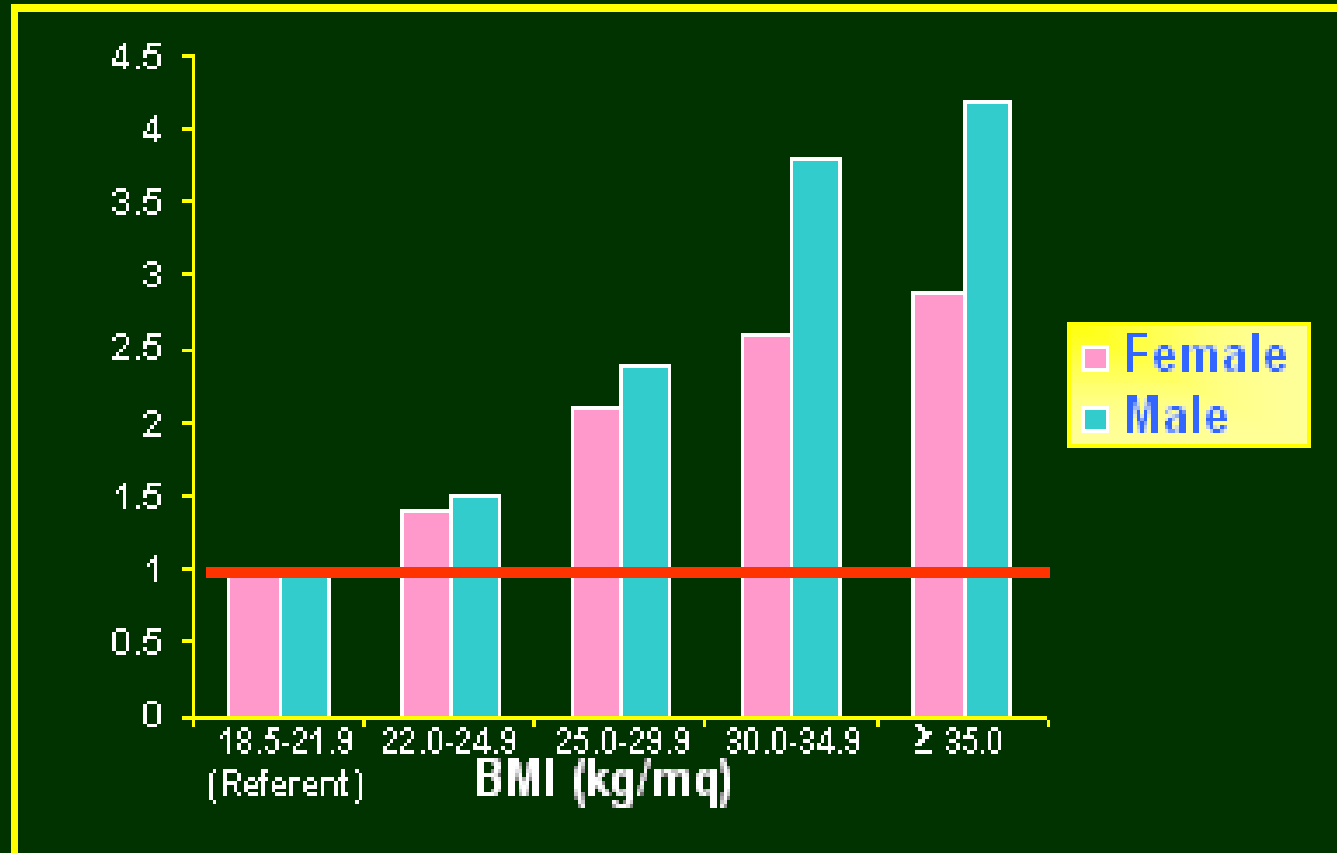
Potentially dangerous Associations

- β -blockers + Clonidine (worsening hypertensive rebounds)
- β -blockers + Non-dihydropyridine Ca₂-antagonists

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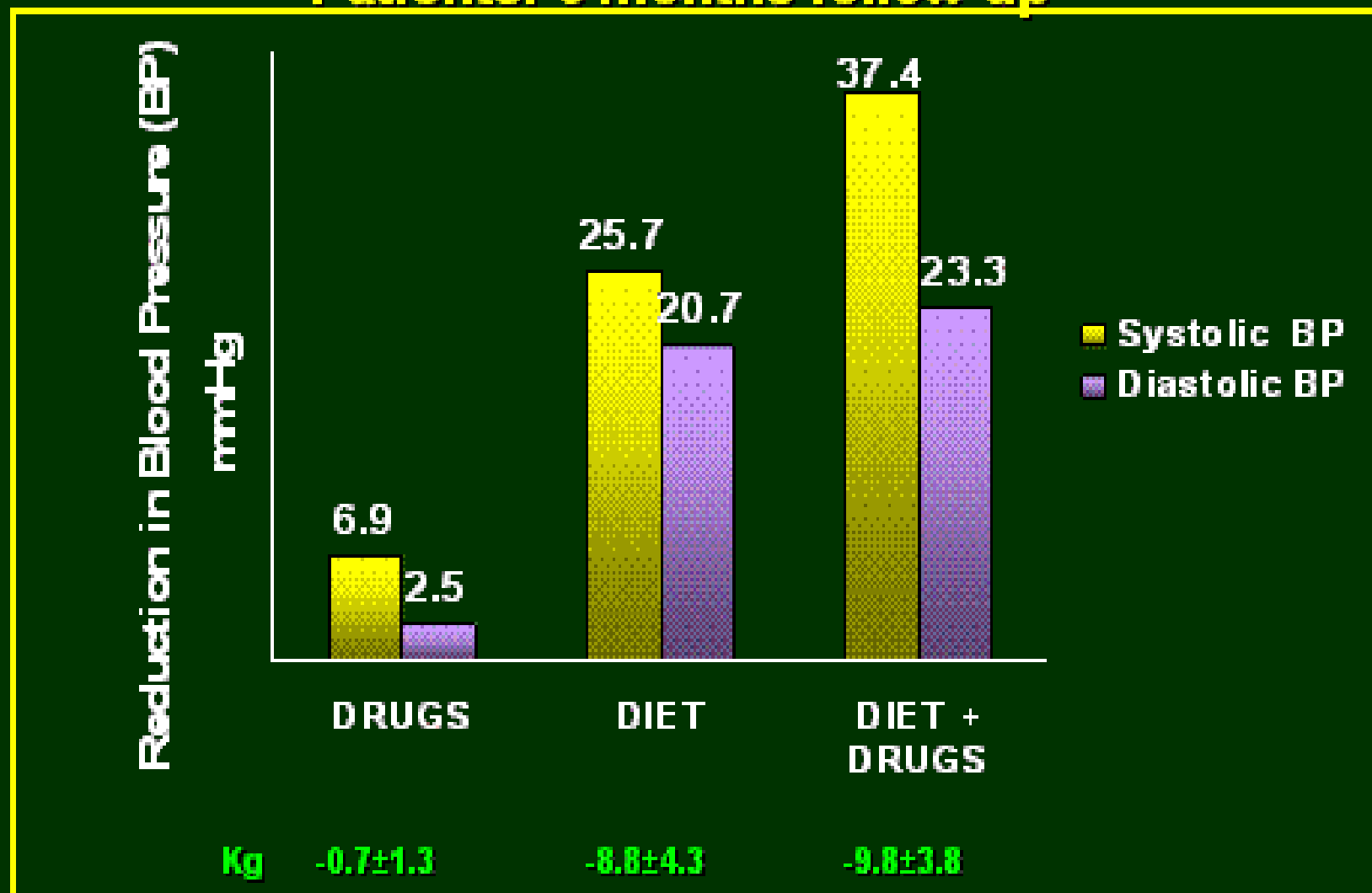
Ten-Year Risk (1986-1996) of Developing Obesity-Related Hypertension Among 77690 Female Nurses and 46060 Male Health Professionals in the United States



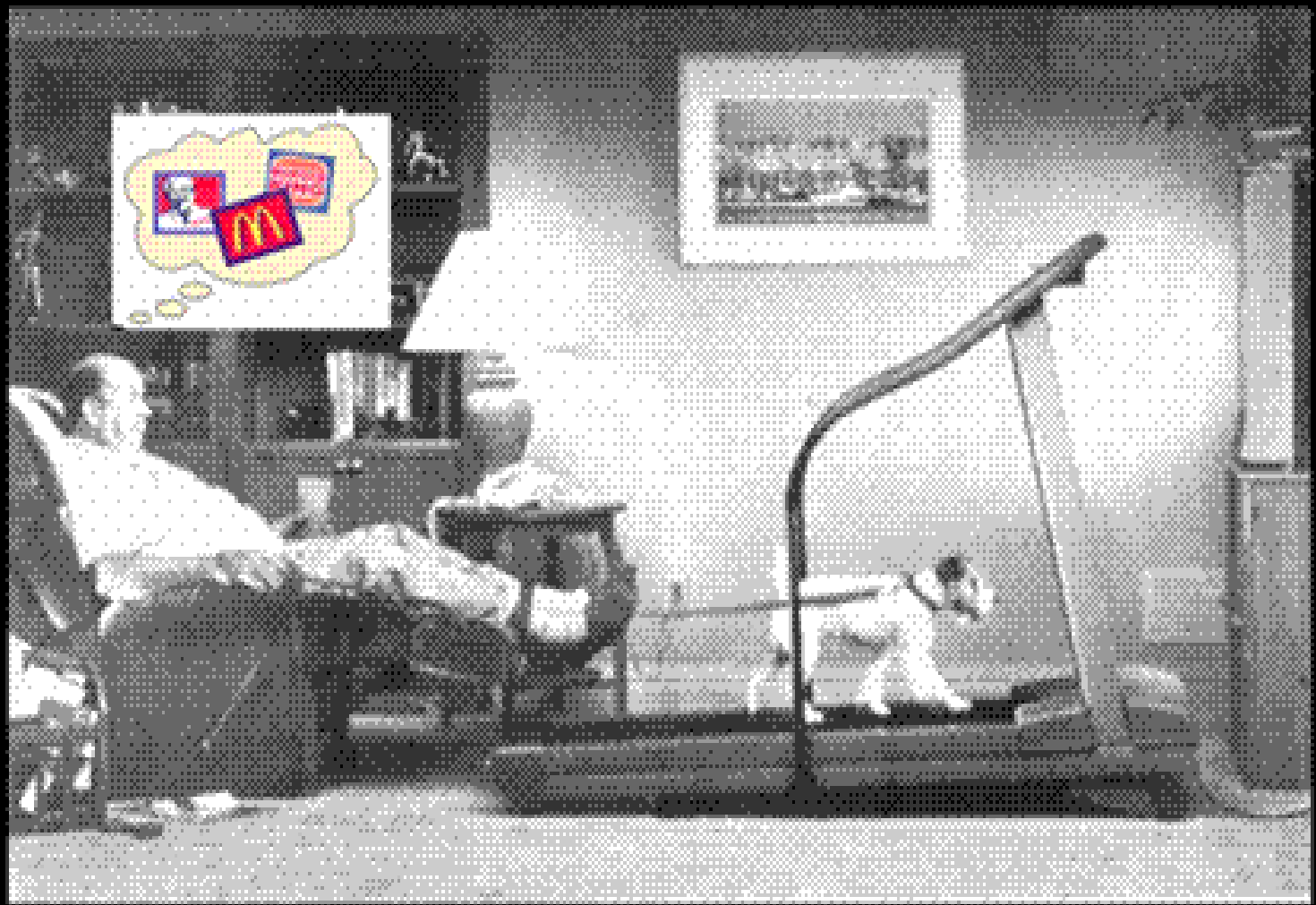
* Adjusted for age, smoking status, and race. CI indicates confidence interval

Adapted from FIELD AE et al, ARCH INTERN MED, 2001

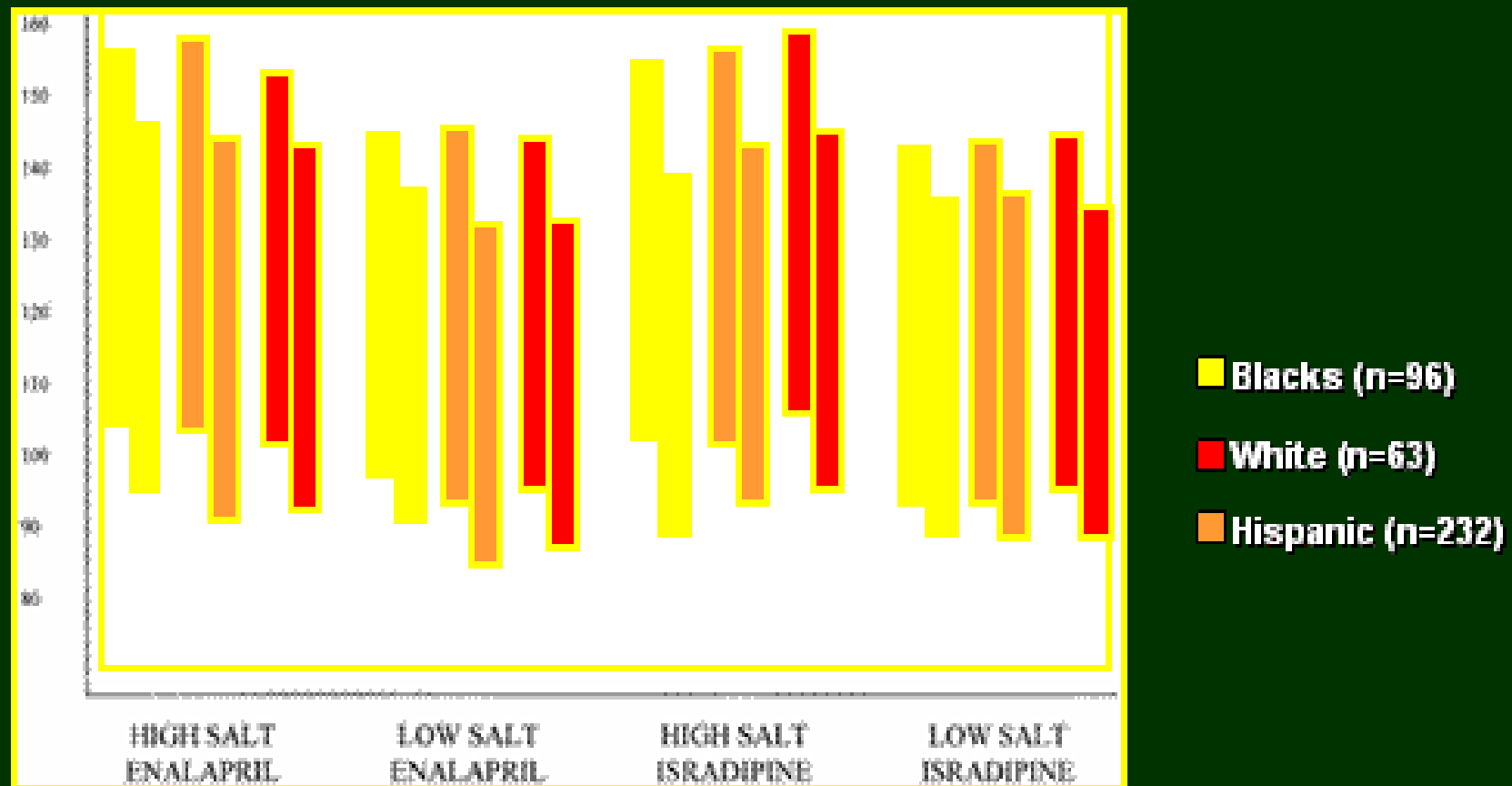
Effect of Weight Loss without Salt Restriction on the Reduction of Blood Pressure in Overweight Hypertensive Patients: 6 months follow-up



Dietary Sodium and Obesity



Effect of salt intake on antihypertensive drugs in salt-sensitive hypertensives



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Iatrogenic Causes of Resistant Hypertension

- ❖ Steroids (corticosteroids, mineralcorticoids, ACTH, anabolic steroids, estrogens)
- ❖ Sympathomimetics (α -stimulants, antiemetics, anti-congestants, MAO-inhibitors, cocaine, amphetamines)
- ❖ NSAIDs, selective COX₂ inhibitors
- ❖ Immunosuppressive drugs (cyclosporine, tacrolimus)
- ❖ Erythropoietin
- ❖ Ma huang, 'herbal ecstasy', and other phenylpropilamine analogs
- ❖ Excessive alcohol or salt intake
- ❖ Natural licorice

In Egypt, the consumption of erk soos (of which licorice is a main constituent) is a common tradition during Ramadan and especially during the warm summer where it acts as a thirst quencher.

The presented case exemplifies one of the common complications of licorice toxicity when a patient without prior medical history presented with severe hypertension, hypokalemia and quadriparesis after prolonged heavy licorice intake.

Ther Adv Endocrinol Metab. 2012 Aug; 3(4): 125–138.
doi: [10.1177/2042018812454322](https://doi.org/10.1177/2042018812454322)

Licorice abuse: time to send a warning message

Licorice-induced mineralocorticoid effect can be abated after cessation of intake, adequate potassium replacement and spironolactone therapy

We emphasize the importance of a thorough and detailed dietary history, including licorice-containing products and herbal medicines

The FDA should start regulating the use of this substance and create public awareness through the media about its health hazards.

We aim to send a warning message that licorice is not just a candy and that serious life-threatening complications can occur with excess use.

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UPRIGHT



AIRWAY OPEN



**Genioglossal EMG:
INSPIRATORY BURSTS**

SUPINE



**TENDENCY OF TONGUE TO RELAPSE
AIRWAY OPEN**



**Genioglossal EMG:
TONIC ACTIVITY
+ INSPIRATORY BURSTS**

SUPINE



**TONGUE RELAPSED AGAINST
POSTERIOR PHARYNGEAL WALL
AIRWAY OBSTRUCTION**



**Genioglossal EMG:
GREATLY DIMINISHED OR
ABSENT ACTIVITY**

Obstructive Sleep Apnea and HTN

- **Obstructive sleep apnea (OSA), is defined as an average of at least 10 apneic and hypopneic episodes per sleep hour**
- **By definition, apneas or hypopneas that last a minimum of 10 seconds are considered clinically significant, although they usually last from 20 to 30 seconds and can last more than one minute**
- **About 10 percent of persons 30 to 60 years of age (5 percent of women and 15 percent of men) have OSA**

Obstructive Sleep Apnea and HTN

- **About 50% of patients with EH have OSA, and about 50% of all patients with OSA have EH**
- **The more severe the OSA, the more prevalent, severe and resistant the hypertension**
- **Successful treatment of OSA is associated with a significant reduction in blood pressure levels**

Potential mechanism by which OSA contributes to the development of resistant hypertension

- **Calhoun et al have demonstrated increased aldosterone excretion in subjects with resistant hypertension and symptoms of sleep apnea**
- **Animal studies suggest that acute hypercapnia or hypoxia separately increase plasma aldosterone concentration independent of increases in plasma renin activity**

Treatment with CPAP

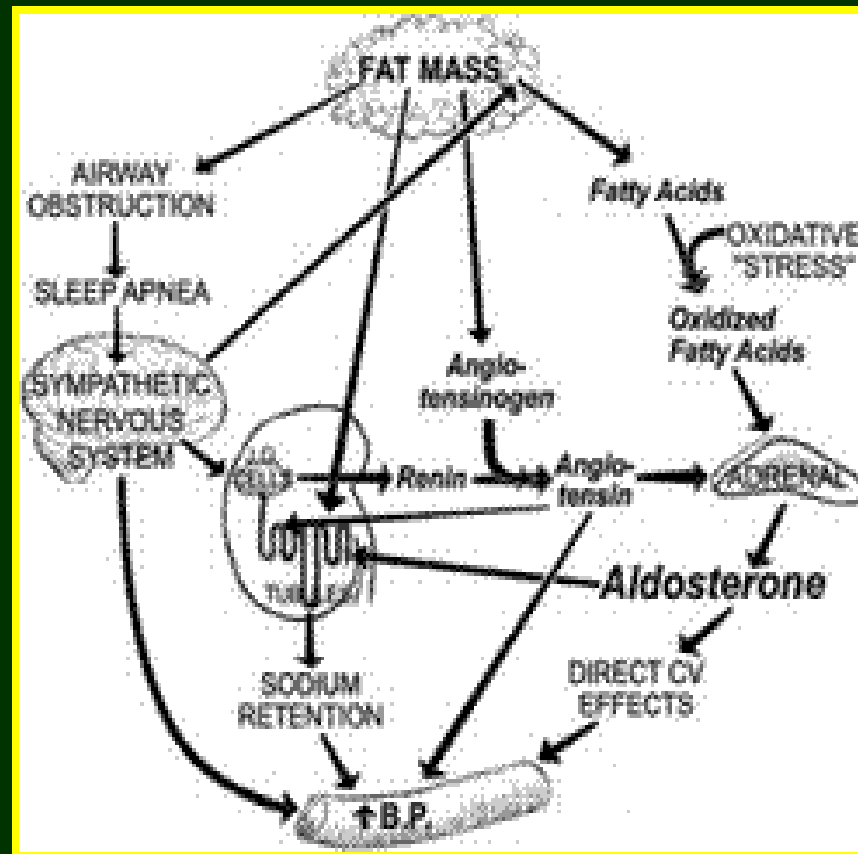
Indeed, if you treat patients with sleep apnea with CPAP, blood pressure goes down.

In normotensive patients, with CPAP nothing happened.

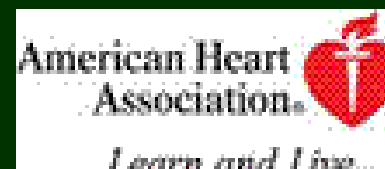
An alternative explanation for the high degree of association between OSA and hyperaldosteronism

- **Obesity and not OSA may be the determinant of the greater aldosterone excretion.**
- **Goodfriend et al suggested that high aldosterone levels in obese hypertensive subjects may be attributable to an adipocyte-derived aldosterone secretagogue independent of renin activity.**
- **The described adipocyte-derived factor is probably an oxidized product of linoleic acid acid**

Real and theoretical links connecting obesity to hypertension



Hypertension



Conclusions

- Non-adherence to anti-hypertensive drugs is a common cause of resistant hypertension
- Often, resistant hypertension is due to an inappropriate regimen (lack of diuretics)
- Several iatrogenic factors (cocaine, alcohol, NSAIDS, etc.) may render HTN resistant to drugs
- Obesity and high salt intake may contribute to resistant hypertension
- Sleep disorders are a common cause of resistant hypertension

Thank You